IN THE HEARINGS AND MEDIATION GROUP OF THE INTELLECTUAL PROPERTY OFFICE OF SINGAPORE REPUBLIC OF SINGAPORE

Singapore Patent No. 51905
19 March 2015

IN THE MATTER OF A PATENT

IN THE NAME OF

GENPHARM INTERNATIONAL INC

AND

APPLICATION FOR REVOCATION THEREOF BY

LONZA BIOLOGICS TUAS PTE LTD

[2015] SGIPOS 13

Hearing Officer: Mr Yeong Zee Kin
IP Adjudicator

Prithipal Singh with Joshua Looi, Uma Baskaran and Adly Rizal (Patrick Mirandah Co.) for the Applicant

Cur Adv Vult

GROUNDS OF DECISION

1 Lonza Biologics Tuas Pte Ltd ("**the applicant**") is the applicant in this matter, seeking a revocation of the Singapore Patent bearing number 51905 ("**the SG 905 patent**" or "**SG 905**"). The proprietor of the SG 905 patent is the respondent, Genpharm International, Inc (US) ("**the proprietor**").

2 The SG 905 patent claims priority from US Patent Number US 5,770,429, which was filed on 10 October 1995 and granted on 23 June 1998. This US patent is a continuation of 13 patents, including an abandoned US patent application 209,741 that was filed on 9 March 1994 ("**the D8 patent**" or "**D8**"). The D8 patent plays a significant role in the applicant's submissions.

3 The SG 905 patent was filed on 10 October 1996 and granted on 16 November 1999. It has been renewed multiple times; with the last renewal on 4 September 2014 and the next renewal due on 10 October 2015.

Applicable Law and Burden of Proof

4 The applicable law is the Patents Act (Cap 221, 2005 Rev Ed) ("**the Act**") and the Patents Rules (Cap 221, 2007 Rev Ed) ("**the Rules**"). Unless otherwise specified, references to rules in these grounds of decision are references from the Rules. The burden of proof in the present case falls on the applicant.

Procedural History

5 The present application for revocation was filed on 19 February 2010. The applicant cites the following grounds (relating to Sections 80(1)(a) and 80(1)(c) of the Act) in its statement of grounds supporting the application for revocation:

(a) Insufficient disclosure of claims 1 and 10;

(b) Lack of novelty in independent claims 1 and 10 and dependent claims 3 – 9 and 11 – 13; and

(c) Lack of inventive steps in claims 1 to 13.

6 The proprietor filed its counter-statement on 21 May 2010. The proprietor sought to maintain the patent and refuted all 3 grounds; additionally, the proprietor proposed the following amendments:

(a) Removal of the term "substantially identical" in the description of the light and heavy chain polypeptide sequences in claims 1 and 10;

(b) Limiting claims 1 and 10 to human immunoglobulin; and

(c) Limiting the claimed human immunoglobulin to be a composition comprising at least one nonhuman animal B cell.

The proposed amendments were published in June 2010. No notice of opposition was filed to the proposed amendments.

7 The applicant filed its evidence in support of its application on 23 August 2010. The proprietor filed its evidence in support of its case on 30 November 2010 (parties agreed to an extension of time). Finally, the applicant filed its further evidence in reply on 28 February 2011.

8 Directions were given for both the applicant and proprietor to file written submissions between March and May 2011. These dealt with the issue of whether the proposed amendments overcame the grounds cited for revocation of SG 905. Eventually, parties agreed to proceed with re-examination on the basis of both the original specifications and the proposed amendments. The proprietor was directed to file an amended counter-statement incorporating the amendments to claims 1 and 10. This was duly filed on 26 August 2011.

Re-examination of SG 905

9 The applicant filed an application for the re-examination of SG 905 pursuant to Rule 81 on 28 September 2011. As detailed in ***Lonza Biologics Tuas Pte Ltd v Genpharm International Inc*** [2014] SGIPOS 9, the re-examination proceeded before the corrections to SG 905 were considered. The re-examination report from the Hungarian Patent Office was issued on 19 November 2012. The findings of the re-examination report may be summarised as follows. On the original claims, the examiner concluded that there was insufficient disclosure and the patent lacked both novelty and inventive step. Considering the amended claims, the examiner concluded that the amendments overcame the challenges on insufficient disclosure and the lack of novelty, but the amended claims were still lacking in inventive step.

Corrections to SG 905

10 On 29 September 2011, the proprietor applied to make a set of corrections to SG 905 in order to replace several occurrences of "affinity" with "avidity" and "affinity constant" with "avidity constant". The applicant objected to these proposed corrections. The details of this contested application are the subject matter of the decision in ***Lonza Biologics Tuas Pte Ltd v Genpharm International Inc*** [2014] SGIPOS 9. For the purpose of this decision, we need only be concerned with the final order of the assistant registrar, which was that:

> 34. The correction of the title of Table 17 is allowable, as is the correction to page 24, line 25. I allow these corrections.
>
> 35. The other proposed corrections are not allowable and therefore I refuse these corrections.

The proprietor withdraws from these proceedings

11 Following the decision concerning corrections, the registrar gave certain directions in order to move the matter towards a hearing. Time lines were set for the filing and exchange of written submissions and for parties to agree on a list of issues.

12 Parties attended a case management conference on 26 February 2015 before me where the dates for the hearing were fixed for 19 and 20 March 2015 and directions given for the taking of evidence from the expert witnesses concurrently (*i.e.* hot tubbing). Subsequently, the registrar was informed by the proprietor that it wished to withdraw from the proceedings. A case management conference was held on an urgent basis on 13 March 2015, during which

the proprietor informed me that it was withdrawing from the hearing and that its expert witness would not therefore be available at the hearing on 19 and 20 March 2015. These intentions were duly noted and the proprietor was informed that it needed to make an election on how it wished to effect this intention. Various options were available to the proprietor: e.g. consent to the present revocation application, offering no further evidence or submissions, taking no further steps in the proceedings, abandonment of the patent, etc. The proprietor elected to withdraw from the hearing and requested that the adjudication proceeds even though it would not be participating in the hearing. The proprietor's wish was for its case to stand on the documents filed. The proprietor was permitted to take its leave from the case management conference on 13 March 2015 and did not appear at the hearing on 19 March 2015.

13 Pursuant to Rule 88A(6) , if a party desiring to be heard does not appear at the hearing:

> the Registrar may proceed with the hearing in the absence of that party, or may, without proceeding with the hearing, give his decision or dismiss the proceedings, or make such other order as he thinks fit.

14 If this were an application commenced by the proprietor, I would have no compunction in dismissing the application forthwith. However, the proprietor is the respondent and the applicant wished to proceed with the hearing. Mindful that a decision granting the application in default is more easily set aside should the proprietor apply under either Rule 88A(9) or (10), it was prudent to proceed with a consideration of the merits of the application and come to a decision on the issues in dispute, after having considered the evidence from the applicant and also the evidence that the proprietor had filed.

Issues To Be Addressed

15 In arriving at my decision, I address the following issues in these grounds. First, the precise specifications of SG 905 that I am to consider. Second, the treatment of the statutory declarations and documentary evidence filed by the proprietor now that it has withdrawn from the proceedings. Third, my detailed findings and conclusions on the issues for which oral evidence was taken.

PRELIMINARY DECISION

Specifications of SG 905 To Be Considered

Proposed amendments to claims 1 and 10

16 There having been no conclusive order concerning the proposed amendments to SG 905, the status of SG 905 was a preliminary issue that I had to deal with before commencing with the hearing proper. Rule 85 does not set out the procedure after advertisement of the proposed amendments but gives the registrar discretion to "give such directions as he may

think fit with regard to any aspect of the procedure for the opposition to the amendment": Rule 85(4). I turn to Rule 52, which deals with the amendment of specifications after the grant of patent, for guidance. Rule 52 sets out a procedure that requires the advertisement of proposed amendments and the filing of oppositions. Rule 52(9) deals with the scenario where, after the proposed amendments have been advertised, no notice of opposition is received. The registrar may give leave for the proposed amendment if he "is satisfied with the reasons for making the proposed amendments." This is the same test that I adopt in considering the proposed amendments in the context of a pending revocation application.

17 The amendments were proposed by the proprietor in its counter-statement. There is nothing in the records to suggest that the offer to amend has been withdrawn. Indeed, the proprietor states in the counter-statement that SG 905 should be maintained subject to these amendments: paragraph 29 of the counter-statement. The amendments were advertised. No objections were received. The amendments were also considered by the patent examiner in the re-examination report. Crucially, the proprietor had stated that it wished for the adjudication to proceed with its case standing on the documents already filed, which would include the proposed amendments in its counter-statement.

18 Turning to the counter-statement, the offers for the amendment were made by the proprietor in a *bona fide* attempt to reduce the issues in dispute by narrowing the scope of its patent claims. In respect of the challenge based on insufficient disclosure, the offer was made to narrow the scope of dispute and in order to expedite the proceedings:

> 5. ... the claimant objects to the term "substantial identity" in claims 1 and 10 for the term is vague and unclear … The defendant disagrees. However, *to expedite the proceedings*, the defendant offers to amend the patent by deleting the term "substantial identity" from claims 1 and 10.
>
> [Emphasis added.]

19 In respect of the challenge based on the lack of novelty, the offer to amend was made in order to overcome the challenge:

> 18. However, in order to distinguish the invention more clearly from the prior art mentioned in the statement, the defendant offers to amend the patent by including the following limitation to claims 1 and 10
>
> "A composition comprising a <u>human</u> immunoglobulin … <u>wherein the immunoglobulin is from at least one nonhuman animal B cell</u>."
>
> *Therefore, the objection is overcome.* …
>
> [Emphasis added.]

20 Indeed, the patent examiner had considered these amendments in the re-examination report and concluded that these were sufficient to overcome challenges on the grounds of insufficient disclosure and lack of novelty:

> 5.5 In summary, it is considered that the amendments proposed by the Proprietor would only partially overcome the grounds of revocation. Accordingly, the grounds of revocation for lack of novelty and sufficient disclosure … would be overcome, but the amended claims would not satisfy the requirement of inventive step …

21 In light of the foregoing, I am satisfied that the offer to amend was made in a *bona fide* attempt to reduce the issues in dispute and to expedite proceedings. At least for the purpose of the re-examination of the patent, the proposed amendments were effective in overcoming two of the grounds of challenge based on insufficient disclosure and lack of novelty. The effectiveness of the offer in reducing the scope of dispute and expediting proceedings is further evidenced by the fact that at the hearing before me, the applicant chose not to offer submissions or expert evidence on the ground of challenge based on lack of novelty.

22 Hence, I am satisfied with the reasons for the proposed amendments and am of the view that leave to amend ought to be granted. I will proceed to consider the arguments of applicant on the basis of amended claims, which I set out below:

> 1. A composition comprising ~~an~~ a human immunoglobulin having an affinity constant (K_a) of at least 2×10^9 M^{-1} for binding to a predetermined human antigen, wherein said immunoglobulin consists of:
>
> > a human sequence light chain composed of (1) a light chain variable region ~~having a polypeptide sequene which is substantially identical to a polypeptide sequence~~ encoded by a human V_L gene segment and a human J_L gene segment, and (2) a light chain constant region ~~having a polypeptide sequence which is substantially identical to a polypeptide sequence~~ encoded by a human C_L gene segment; and
> >
> > a human sequence heavy chain composed of (1) a heavy chain variable region ~~having a polypeptide sequene which is substantially identical to a polypeptide sequence~~ encoded by a human V_H gene segment, optionally a D region, and a human J_H gene segment, and (2) a constant region ~~having a polypeptide sequence which is substantially identical to a polypeptide sequence~~ encoded by a C_H gene segment;
> >
> > wherein the immunoglobulin is from at least one nonhuman animal B cell.
>
> …
>
> 10. An isolated human immunoglobulin having an affinity constant (K_a) of at least 1×10^{10} M^{-1} for binding to a predetermined human antigen, wherein said immunoglobulin consists of:
>
> > a human sequence light chain composed of (1) a light chain variable ~~region~~ [*sic*] ~~having a polypeptide sequene which is substantially identical to a polypeptide sequence~~ encoded by a human V_L gene segment and a human J_L gene segment, and (2) a light chain constant region ~~having a polypeptide~~

~~sequence which is substantially identical to a polypeptide sequence~~ encoded by a human C_L gene segment; and

a human sequence heavy chain composed of (1) a heavy chain variable region ~~having a polypeptide sequene which is substantially identical to a polypeptide sequence~~ encoded by a human V_H gene segment, optionally a D region, and a human J_H gene segment, and (2) a constant region ~~having a polypeptide sequence which is substantially identical to a polypeptide sequence~~ encoded by a human C_H gene segment;

wherein the immunoglobulin is from at least one nonhuman animal B cell.

Correction to description of Table 17

23 For completeness and ease of reference, the descriptions of table 17 that are found on pages 24 and 247 had been corrected – following the decision of the assistant registrar in ***Lonza Biologics Tuas Pte Ltd v Genpharm International Inc*** [2014] SGIPOS 9 – to read as follows:

Table 17. Rate and avidity ~~affinity~~ constants for monoclonal antibodies that bind to human CD4.

Evidential Issues

24 Before considering the submissions on the substantive issues, there are a few evidential issues that have to be dealt with. First, the admissibility of the statutory declaration of the proprietor's expert dated 29 November 2010 that was filed in reply to the applicant's evidence in support of the application. Since the proprietor has withdrawn from the hearing and is not offering its expert witness for cross-examination, how should this statutory declaration be treated? Second, the proprietor had filed expert evidence in the form of two prior art documents in support of its counter-statement. How should these documents be treated in light of the first evidential issue? Lastly, the treatment of the re-examination report in my assessment of the evidence from the applicant's expert.

Admissibility of the statutory declaration of the proprietor's expert witness

25 The applicability of the Evidence Act (Cap 97, 1997 Rev Ed) to hearings conducted before the registrar is a preliminary issue that I have to deal with. The Evidence Act and the Rules of Court (Cap 322, 2014 Rev Ed) apply to judicial proceedings before the courts but not otherwise: see section 2(1) of the Evidence Act and Order 1, Rule 2 of the Rules of Court. However, parties can by agreement adopt these evidential rules. If parties agree that the Evidence Act should apply to the hearing, the Rules of Court are likewise implicitly adopted: ***Martek Biosciences Corp v Cargill International Trading Pte Ltd*** [2011] 4 SLR 429; [2011] SGHC 71, at [39].

26 Following a case management conference on 15 October 2014, the applicant wrote to the proprietor on 5 November 2014 proposing a list of issues for this hearing; they also proposed that the Evidence Act should apply to the hearing:

> For the sake of expediency, unless we hear from you to the contrary, we shall take it that the Evidence Act (Cap 97) applies to the proceedings herein.

27 A response was sought from the proprietor, who replied on 14 November 2014 dealing only with the list of issues. The proprietor did not raise any objections to the application of the Evidence Act to these proceedings in this correspondence. The applicant submits that no objections had been raised by the proprietor to the application of the Evidence Act to these proceedings in any of the subsequent correspondence, nor at any case management conferences; or indeed when they appeared at this hearing (*i.e.* before they took their leave).

28 To my mind, the proposal from the applicant clearly puts an obligation on the proprietor to raise any objections that it may have to the application of the Evidence Act to these proceedings. Notwithstanding how the applicant phrased the proposal, it was nevertheless an offer and although there is no express acceptance, I think that there was acceptance by acquiescence and conduct. The proprietor took subsequent steps to prepare the matter for hearing:

(a) Parties settled the list of issues by correspondence;

(b) Written submissions were exchanged on 15 December 2014;

(c) Parties attended a case management conference on 26 February 2015 during which dates of this hearing were fixed and directions were given for the taking of concurrent evidence from both parties' expert witnesses;

(d) During the conference on 26 February 2015, an application to tender a further statutory declaration exhibiting the curriculum vitae of the applicant's expert was allowed and in so doing, the practice of the courts was adopted and the proprietor was permitted to cross-examine on this new evidence at the upcoming hearing; and

(e) A further case management conference on 13 March 2015 during which the proprietor informed me of its intention to withdraw from the hearing.

29 I take the case management conference on 26 February 2015 to be of some significance. The discussions and directions for the taking of evidence from the parties' experts concurrently were made in reliance on Order 40A, rule 6 of the Rules of Court. Apart from giving directions for the taking of expert evidence concurrently, parties also discussed how the tribunal chambers were to be reconfigured and where the experts and parties' patent agents and solicitors were to be seated during the hearing.

30 Equally, in arguing the application to tender an additional statutory declaration exhibiting the applicant's expert witness's *curriculum vitae*, the applicant proceeded on the basis that the practice of the courts was applicable and argued that there was no prejudice due to the late production of the *curriculum vitae* of its expert as the proprietor would have the opportunity to cross-examine him on his qualifications at the upcoming hearing. No objections were raised to adopting this procedure.

31 By failing to raise objections when the onus was so clearly placed on them to do so and taking these subsequent steps to prepare for this hearing, the proprietor's conduct amounted to an unequivocal acceptance of the applicant's proposal. Therefore, I have no doubt in my mind that the proprietor had accepted by acquiescence and conduct the applicant's proposal for the application of the Evidence Act to these proceedings.

32 The effect of the application of the Evidence Act has been stated categorically in ***Martek Biosciences Corp v Cargill International Trading Pte Ltd***, at [39]:

> As far as the Respondent's experts' testimony goes, the Respondent chose to withdraw Dr Puah from cross-examination, … I should make it clear that the withdrawal of Dr Puah from cross-examination means that his evidence should bear no weight at all. Order 38 r 1(2) of the Rules of Court (Cap 322, R 5, 2006 Rev Ed) makes it clear that a witness's affidavit will not be received in evidence if he is not cross-examined, except with leave of court. Of course, O 38 r 1(2) applies to actions commenced by writ, not usually to hearings before IPOS. However, in my view O 38 r 1(2) should apply with equal force here, with the witnesses' statutory declarations analogous to affidavits in a trial. The parties agreed at a Case Management Conference on 6 February 2009 that the Evidence Act (Cap 97, 1997 Rev Ed) would apply to their proceedings and implicitly the Rules of Court too by virtue of s 137 of the Evidence Act. *In any case, whether in a trial or in IPOS proceedings, it would clearly prejudice the Applicant for the Respondent to refuse to present its main witness for cross-examination, especially at the last minute, and still seek to keep that witness's statutory declaration on record.* I take cognisance of the Applicant's argument before me that r 80 of the Patents Rules leaves open the procedure of revocation proceedings and therefore it is important for this case to clarify the evidential consequences of irregularities such as the one here. In my view, where parties have clearly agreed to conduct IPOS proceedings like court trials, namely, applying the Evidence Act and the Rules of Court, they must abide by the principles governing court trials.
>
> [Emphasis added.]

33 My reading of this passage is that it is authority for the following propositions insofar as proceedings under the Rules are concerned. The first is this. Where parties have expressly adopted the Evidence Act, the Rules of Court are likewise incorporated by virtue of section 137 of the Evidence Act. Pursuant to this, Order 38, rule 2(1) operates to exclude the affidavit of a witness who fails to attend the hearing, unless the court gives leave to accept the affidavit.

34 The second is this. The italicised sentence in the passage quoted above is authority for the proposition that the exclusion of the written testamentary evidence of witnesses (whether in the form of an affidavit or statutory declaration) who do not appear before a tribunal, coupled with a discretion to accept, is a general principle of the law of evidence that applies to proceedings under the Rules. The mischief that this principle of evidence law is intended to address is the prejudice to the adverse party who is deprived of the opportunity to cross-examine the absent witness. The applicant's counsel reminded me that the right to test your opponent's evidence through cross-examination is a fundamental feature of our adversarial system, as encapsulated by the Court of Appeal's pronouncement in ***Teo Wai Cheong v Crédit Industriel et Commercial and another appeal*** [2013] 3 SLR 573; [2013] SGCA 33:

> 25 … It is a truism that cross-examination plays a fundamental role in the common law's adversarial process for getting to the truth. The jurist John Henry Wigmore went so far as to declare that "it is beyond any doubt the greatest legal engine ever invented for the discovery of the truth" (see John Henry Wigmore, *A Treatise on the Anglo-American System of Evidence in Trials at Common Law* (1905) … at para 1367).

35 Insofar as revocation proceedings are concerned, Rule 80(10) is the doorway through which this evidential principle is received. I wish only to add the following observations. The modern use of written testamentary evidence developed as a procedure for a more efficient way to adduce the witness' evidence-in-chief. It is also a procedure designed for modern civil litigation which is conducted with the proverbial cards placed open on the table. Historically, before the prevalent use of written testamentary evidence, the oral testament of a witness who does not attend the hearing can only be received in exceptional circumstances. Such a statement – whether oral or written – stands as an out-of-court statement that is inadmissible by reason that it is hearsay evidence. It can only be accepted into evidence if one of the hearsay exceptions apply, e.g. *ipsissima verba* or section 33 of the Evidence Act. The historical balance of substantive justice cannot be unhinged by modern procedures designed for efficiency and disclosure. Hence, the written testamentary evidence of an absent witness should not be received unless there are exceptional circumstances that provide an exception to hearsay.

36 On this preliminary issue, my conclusion therefore is this. I find that the proprietor's conduct in failing to raise objections to the offer to apply the Evidence Act that was couched in terms that placed the onus on it to do so, coupled with its conduct in taking steps to advance the matter for hearing – in particular, taking directions for the recording of expert evidence concurrently in accordance to procedures set out in the Rules of Court – is sufficient to amount to an acceptance by acquiescence or conduct. In the event that my finding is erroneous, Rule 80(10) gives me a discretion to direct that the statutory declaration of the proprietor's expert witness be disregarded. I do so direct for the reason that the statutory declaration is hearsay and to receive it would prejudice the applicant by depriving it the opportunity to cross-examine the absent expert witness.

Treatment of the expert evidence filed by the proprietor

37 Having dealt with the statutory declaration of the proprietor's expert witness, I turn now to the remaining prior art documents that had been filed in support of the counter-statement:

(a) RR Porter, "Structural Studies of Immunoglobulins" *Nobel Lecture,* 12 December 1972; and

(b) Bruce Lamb & John Gearhart, "YAC transgenics and the study of genetics and human disease" *Current Opinion in Genetics and Development 1995*, 5:342–348.

38 These scientific articles are cited by the proprietor to show the state of the general knowledge at the time of their invention. *Porter* is cited to show that it was common general knowledge that an immunoglobulin comprises at least two light chains and at least two heavy chains; *Lamb & Gearhart* is cited as a description of the technical difficulties facing researchers in YAC transgenesis, in particular the perceived advantages of the microinjection technique and the technical difficulties that had yet to be overcome.

39 The treatment of these prior art documents are circumscribed by the following considerations. First, the prior art are in the nature of documentary expert evidence from third party sources and should be treated with less circumspection than the oral testamentary evidence of an expert witness appointed by a party to the proceedings. The prior art documents, in and of themselves, are objective and neutral. It is *how* the proprietor chooses to rely on them that is presumably partisan.

40 Second, these form part of the proprietor's counter-statement and have to be considered in order to appreciate the defence that it seeks to mount against the revocation challenge. The proprietor having withdrawn from these proceedings and electing to rest its case on documents already filed, and there being no application or good reason to expunge its counter-statement and its annexures, they remain on the record and form part of the documents in the possession of the registrar. In the case where no counter-statement is filed, Rule 80(4) requires the registrar to consider the revocation application on the basis that "each specific fact set out in the statement were conceded, except in so far as it is contradicted by other document in [his] possession"; *a fortiori*, in the present case where the proprietor withdraws before the hearing and rests his case on documents already filed, these prior art documents are in the possession of the registrar and therefore the expert evidence adduced by the applicant has to be considered and weighed against them.

41 Third, these prior art documents are to be considered only to the extent that they have been offered as objective descriptions of the state of the art and the technical challenges facing persons in this field of research. I am reminded of the Court of Appeal's admonition in ***Poh Soon Kiat v Desert Palace Inc (trading as Caesars Palace)*** [2010] 1 SLR 1129; [2009] SGCA 60 that one cannot blindly accept expert evidence, even if unchallenged, but to evaluate it with the same care and detail as any other evidence:

The rule of prudence with regard to expert evidence

22 In ***Saeng-Un Udom v PP*** [2001] 2 SLR(R) 1, this court observed that a judge must not blindly accept expert evidence on any matter merely because that evidence was not contradicted (at [26]-[27]). In ***Sakthivel Punithavathi v PP*** [2007] 2 SLR(R) 983 ("*Sakthivel Punithavathi*"), V K Rajah JA reiterated this rule (at [76]) as follows:

> What is axiomatic is that a judge is not entitled to substitute his own views for those of an uncontradicted expert's: *Saeng-Un Udom v PP* [2001] 2 SLR(R) 1. Be that as it may, a court must not on the other hand unquestioningly accept unchallenged evidence. Evidence must invariably be sifted, weighed and evaluated in the context of the factual matrix and in particular, the objective facts. An expert's opinion 'should not fly in the face of proven extrinsic facts relevant to the matter' per Yong Pung How CJ in ***Khoo James v Gunapathy d/o Muniandy*** [2002] 1 SLR(R) 1024 at [65]. In reality, substantially the same rules apply to the evaluation of expert testimony as they would to other categories of witness testimony. Content credibility, evidence of partiality, coherence and a need to analyse the evidence in the context of established facts remain vital considerations; [the expert witness's] demeanour, however, more often than not recedes into the background as a yardstick.

42 As the proprietor offers no expert witness to articulate how else these prior art documents may be relevant, I am limited to relying on them only to the extent as they are pleaded in the counter-statement. I can nevertheless rely on these prior art documents to test the oral testimony of the applicant's expert witness in order to ensure that the expert opinion is sound and that there is no contradiction that cannot be explained.

Treatment of the re-examination report

43 One final evidential issue that ought to be considered is the treatment of the re-examination report ordered pursuant to Section 80(2) of the Act and Rule 81. The starting point is that I have to "take into consideration the conclusions of the re-examination report in making [my] determination on the patent or the patent as amended": Rule 82. In ***Martek Biosciences Corp v Cargill International Trading Pte Ltd*** [2011] 4 SLR 429; [2011] SGHC 71 and ***Martek Biosciences Corp v Cargill International Trading Pte Ltd*** [2012] 2 SLR 482; [2012] SGHC 35, the value of the re-examination reports was greatly diminished for several reasons. First, the re-examination reports were made in reliance on the statutory declarations of expert witnesses without any opportunity for cross-examination. Second, the respondent in these cases had two experts, one of whom was withdrawn from cross-examination during the hearing and it was established that the remaining expert witness had admitted that his expertise was not specific to the field of science that case was concerned with. In light of these developments, the court had concluded that the value of the re-examination report in that case was greatly diminished.

44 There are a number of similarities with the present case. The re-examination report was prepared on the basis of the statutory declarations of both parties' experts and without

the benefit of cross-examination. There was no opportunity for cross-examination of the proprietor's expert before the patent examiner who prepared the re-examination report as it was prepared based on a review of the statutory declarations filed by the parties. The re-examination report was prepared in reliance on the statutory declaration of the proprietor's expert, which has now been excluded from the hearing and without the benefit of the forge of cross-examination.

45 There are also differences, one of which lies in that the credentials and expertise of the proprietor's expert have not been challenged in the present case. This is unsurprising as the conclusion of the re-examination report is relied on by the applicant to support its case for revocation. It is to the applicant's advantage to persuade me to accept the re-examination report and to adopt its conclusions.

46 Unlike ***MacDermid, Incorporated v Alpha Fry Limited*** [2009] SGIPOS 13, I do not have the luxury of adopting the conclusions of the re-examination report *in toto*. I must, nevertheless, take it into consideration as mandated by Rule 82 in coming to my decision, in order to ensure that there is no inconsistency that cannot be explained. However, I must also be mindful of those conclusions and portions of the re-examination report that rely too heavily on the excluded statutory declaration of the proprietor's expert witness.

Detailed Findings and Conclusions for Issues in Dispute

47 I turn now to the hearing on 19 March 2015. The applicant called a single witness. He was their expert witness Dr Mahendra Deonarain, a senior lecturer at the Faculty of Natural Sciences in the Imperial College of the University of London. Dr Deonarain tendered three statutory declarations: the first, dated 25 February 2011 was admitted and marked as 'PS 1'; the second, dated 19 August 2010 was admitted and marked as 'PS 2'; and the third, dated 2 March 2015 was admitted and marked as 'PS 3'. A core bundle of documents in two volumes was also tendered, admitted and marked.

48 Dr Deonarain began with an explanation of the science required to understand the SG 905 patent. Immunoglobulins are protein molecules that are often also referred to as antibodies. Antibodies are a crucial component of our bodies' natural immune system. Antibodies function by binding to antigens, *e.g.* bacteria or viruses, which are harmful to our bodies. In doing so, they render the antigens harmless to the human body. Antibodies can take many forms. We are concerned with a Type G immunoglobulin in SG 905 which takes a form that is in the shape of a 'Y'. The central structure of the antibody is formed by two high density long chains (also referred to as heavy chains). These are joined at the lower part of the 'Y' structure to form its trunk, before branching at the upper part of the structure to form the two arms of the 'Y' structure. On each of these arms, there is one low density short chain (also referred to as light chains). Hence, the Type G antibody comprises of two heavy chains and two light chains.

49 The effectiveness of an antibody lies in its binding site. The binding sites of Type G antibodies are on each arm of the 'Y' structure. As noted above, each arm comprises of a

light chain and part of a heavy chain. As these are protein molecules, the building blocks are amino acids. The sequence of amino acids on these protein molecules are determined by genetic material (DNA or RNA). Naturally occurring DNA and RNA in an organism (like a mouse) will produce a natural sequence. By introducing genetic material from a different organism, it is possible to change the sequence and type of amino acids on the antibody. An antibody that is thus produced is referred to as transgenic.

50 The purpose of creating transgenic antibodies is to improve the effectiveness of their binding sites. The effectiveness of an antibody is determined by the number of binding sites and the binding strength of each binding site. SG 905 is about the creation of transgenic antibodies with high binding strength at each of the binding sites located on the arms of its 'Y' structure.

51 Binding strength is measured in K_a, which measures either avidity or affinity. Avidity binding occurs when an antibody binds to a single antigen. Avidity is influenced by the structure of the antibody (i.e. the more binding sites there is, the stronger the bond) and also the density of the binding sites on the surface of the antigen (denser binding sites on the surface of the antigen increases the number of successful bonds between the antibody and the antigen). For the Type G antibody that we are concerned with in SG 905, this means that both of its arms attach to the single antigen, blocking the antigen's ability to cause harm. This influences the strength of the bond.

52 Affinity binding occurs when an antibody binds to more than one antigen. In the case of the Type G antibody that is the subject matter of SG 905, there can only be a maximum of two antigens thus bound, one to each of its two binding sites. Each binding site on each arm of the antibody works independently to seek out antigens to which it binds. As each binding site attaches to a single antigen, the strength of the bond is weaker. It stands to reason that binding strength that measures avidity will be therefore be higher than binding strength measuring affinity. A higher binding strength is represented by a higher K_a value. This will become crucial in the discussion of the issues below. A major plank of the applicant's case is that SG 905 claims high affinity binding, but the data that they show only illustrate high avidity binding.

53 Dr Deonarain proceeded to explain the essence of the invention in SG 905. The ultimate goal is to raise human antibody against human antigens for therapeutic purposes. SG 905 describes a process whereby human genes are introduced into a mouse and its natural antibodies are knocked out. The mouse's B cell then produces the transgenic antibodies. These antibodies are purified to 90% and the binding strength is tested. SG 905 describes how the human YAC gene is introduced into a mouse. The resulting mouse is referred to as a KCo5 mouse.

54 I turn now to consider the grounds of challenge that were pursued by the applicant at the hearing before me: insufficient disclosure and lack of inventive step.

MAIN DECISION

Ground of Revocation under Section 80(1)(c)

55 Section 80(1)(c) of the Act reads:

> 80. —(1) Subject to the provisions of this Act, the Registrar may, on the application of any person, by order revoke a patent for an invention on (but only on) any of the following grounds:
>
> …
>
> (c) the specification of the patent does not disclose the invention clearly and completely for it to be performed by a person skilled in the art;
>
> …

Insufficient Disclosure

56 The gist of the applicant's challenge on insufficient disclosure is that if a reasonably skilled technician were to follow the methods described in SG 905, the resulting antibody will not have the high affinity binding strength that is claimed. Dr Deonarain drew my attention to table 17 in example 39 and the preceding text which described the following method:

> Human sCD4 (2500 to 4200 RU) was immobilized by covalent coupling through amine groups to the sensor chip surface according to manufacturer's instructions. Antibody dilutions were flowed over the antigen-coupled sensor chips until equilibrium was reached, and then buffer only was allowed to flow.

57 Dr Deonarain explained that this method of attaching the antibody to a biosensor operates by binding the truck of the 'Y' structure to the biosensor thereby exposing the two arms. When the antibody solution is flowed across the surface of the biosensor, each arm of the antibody attaches to a different antigen. The binding that takes place based on the process disclosed is *affinity* binding. Following the correction of the description to table 17, what table 17 is supposed to show are rate and *avidity* constants. The K_a values in table 17 are high, within the range expected of avidity binding strength (i.e. $x \times 10^9 – x \times 10^{10}$). However, there is a disjoint between the *avidity* K_a values in table 17 and the *affinity* binding process that is described in this part of the specifications.

58 Dr Deonarain drew my attention next to table 18 in example 40 to further buttress his point. The description was that of a process that gave rise to affinity binding:

> The rate and equilibrium constants presented in Table 18 were determined with a BIAcore (Pharmacia Biosensor) using goat anti-human IgG (Fc-specific) coupled to the sensor chip and flowing a saturating concentration of mAb over followed by various concentrations of antigen (rCD4).

59 Dr Deonarain explained that this describes a process to capture human antibody by using goat antibody that recognises the human antibody. The goat antibody is coupled to the surface of the sensor chip and when human antibodies are flowed over it, the goat antibodies will capture the human antibodies. The trunk of the 'Y' structure of human antibodies are

bound to the goat antibodies which are in turn coupled to the surface of the biosensor. The binding arms of the 'Y' structure of the human antibodies are exposed. When antigens are flowed across the human antibodies, the binding sites on the arms of the human antibodies will bind with the antigens. This process measures affinity. Dr Deonarain explains that in the case of table 18, the description is correct as it states that the table shows affinity and rate constants. The K_a values in table 18 are about two orders of magnitude lower (i.e. $x \times 10^7 – x \times 10^8$) than those in table 17. Dr Deonarain explains that this is correct as affinity values should be within this range. He goes on further to state that the specifications in SG 905 did not generate any antibodies that had the high affinities as claimed. All they managed to generate were antibodies with affinities of $x \times 10^7 – x \times 10^8$.

60 Dr Deonarain also explained that SG 905 claimed that the proprietor was able to achieve affinity values of *at least* $x \times 10^9 – x \times 10^{10}$. The proprietor is in effect saying that there are no upper limits. With the correction of table 17, the proprietor could not even meet these levels, let alone exceed them. Dr Deonarain opined that the proper thing for the proprietor to have done was to demonstrate the upper limits of what it could achieve and to claim only up to such limit. This would allow the reader to understand the limits of the method that is taught by SG 905. Alternatively, they should have supporting data to show that affinity values can be increased in order to show the potential of the method that is taught. This would require disclosure of data that demonstrate increasing affinity. It is not acceptable to claim that there is no upper limit without doing so and expect the reader to carry out experiments in order to discover where the upper limits lie.

61 Dr Deonarain also pointed out that SG 905 only disclosed data concerning the CD4 human globular protein. The phrase "predetermined human antigens" in Claims 1 and 10 suggests that methods disclosed in SG 905 can raise antigens against any targets. There are many other antigen targets with differing properties: some have flat surfaces or grooves, others are hydrophobic or hydrophilic. The proprietor should disclose data beyond globular protein in the specifications before making such broad claims.

62 At this juncture, I should point out that although insufficient disclosure was a pleaded ground of challenge, these particulars were not articulated before this hearing. A perusal of the applicant's statement of grounds for their revocation application discloses that the particulars for the ground of challenge for insufficient disclosure were the lack of clarity of the term "substantially identical" and the lack of clarity and support on the definition of the term "immunoglobulin". Unsurprisingly, the proprietor's response in its counter-statement was addressed to these areas. Similarly, the patent examiner's focus in the re-examination report was on these two terms. The documents on record therefore provided no assistance.

63 In order for me to evaluate the opinion of Dr Deonarain, I proceeded to consider the remaining tables that disclosed binding values, i.e. tables 19 – 21. After describing the affinity method that led to affinity values disclosed in table 18, example 40 proceeds to describe what I understand to be an avidity method:

> The rate and equilibrium constants presented in Table 19 were determined with a BIAcore, using antigen (fCD4) coupled to the sensor chip and flowing mAB over.

64 I understand this process to involve a biosensor with antigens on its surface. When the solution containing antibodies is flowed over the biosensor, each arm of the antibody will bind to an antigen. Once one arm is bound, the remaining arm will likewise seek a binding site on the antigen. This describes avidity binding and the values in table 19 show avidity binding constants in the range of $x \times 10^9 - x \times 10^{10}$. This is consistent with the avidity constants that are shown in table 17.

65 Table 20 shows the range of avidity constants that are reported by other researchers in their publications. The range is wide: $x \times 10^7 - x \times 10^{11}$. Apart from the description, SG 905 does not explain the significance of this set of figures. I am therefore unable to draw any conclusions from this except for the following observation: of the 7 avidity values shown, 5 were in the range of $x \times 10^9 - x \times 10^{11}$. This corroborates Dr Deonarain's assertion that avidity values are usually higher.

66 Example 40 concludes by describing one further process. Table 19 showed results when recombinant CD4 was used as an antigen (i.e. artificially created in a laboratory environment). In order to compare the avidity binding strength of naturally occurring CD4, the method described involved serial dilutions of antibody and incubation with a binding assay (SupT1 cells). After washing, bound antibodies are detected by using conjugated goat anti-human antisera. Based on my understanding of this process, it would appear that avidity binding is achieved. When the antibody and natural CD4 antigens are incubated in a solution, the antibody will seek out the antigen. Since the antibody is free, once one of its arms binds to the antigen, the remaining arm will be able to seek out a binding site on the same antigen. Hence, both arms of the antibody will bind to the same antigen. This is avidity binding and the avidity values in table 21 are in the same order of magnitude as those in table 19.

67 From the foregoing, I am of the view that Dr Deonarain's explanation is credible and provides a coherent explanation of the binding values that are disclosed in tables 17 to 21. It also consistently explains the binding values to be expected from either an avidity or affinity binding. The specifications also corroborate Dr Deonarain's critique that the disclosed experiments related only to CD4 human globular protein, whether recombinant or naturally occurring. I therefore accept Dr Doenarain's expert opinion.

68 However, there is one further issue that I ought to address. The particulars of challenge that Dr Deonarain spent time during the hearing to explain were not the same particulars that were pleaded in the statement of grounds for the revocation application. In the statement of grounds, the particulars relied on for the challenge based on the ground of insufficient disclosure were the lack of clarity of the term "substantially identical" and the lack of clarity and support for the definition "immunoglobulin". Were the present particulars, premised on the failure to disclose all necessary steps, newly introduced only at the hearing? Admittedly, the proprietor had withdrawn from the hearing and it had to accept the risk that the grounds of challenge may be altered. However, for reasons that I shall soon explain, I do not think that there is any prejudice to the proprietor.

69 Perusing the statutory declaration of Dr Deonarain PS 2, I note that as early as 19 August 2010 when this statutory declaration was made, he had already highlighted these issues. Dr Deonarain had described that SG 905's "most immediately recognizable improvement to Lonberg (D8) is to overcome the problem of generating higher affinity antibodies." At that time, Dr Deonarain had opined that claims 1 and 10 of SG 905 do not show that the KCo5 transgenic mice were directly responsible for a general increase of antibody affinity. The following passage from PS 2 is of some significance:

> **8. From the disclosure in SG 51905, is it possible to create <u>all</u> human antibodies with an association binding affinity constant (Ka) of <u>at least</u> 2×10^9 M^{-1} (Claim 1) and <u>at least</u> 1×10^{10} M^{-1} (Claim 10)?**
>
> The antibodies in Claims 1 + 10 have an association binding affinity constant (K_a) of at least 2×10^9 M^{-1} (Claim 1) and 1×10^{10} M^{-1} (Claim 10). This suggests that affinities reading 10^{15} M^{-1} or even 10^{20} M^{-1} are also claimed, *which are currently impossible or unobtainable in the literature*.
>
> [Emphasis added.]

70 At the time PS 2 was made, the correction to the description of table 17 had not yet been made. Table 17 was then described as showing affinity binding values. Dr Deonarain had opined that since the proprietor could only demonstrate high affinity binding values for example 39 in table 17, they should have limited their claim to this example instead of making a more general claim and relegating this to an example. He reasoned that the generality of the claims meant that affinity values above those specified in the claims were also part of the invention that was claimed by SG 905. Hence, the words in emphasis in the quoted passage meant that the SG 905 patent specifications did not disclose a method that could yield affinities higher than the values that were stated in table 17. Put simply, at that time when table 17 was understood to disclose affinity values, the applicant had already challenged that the disclosures in SG 905 did not yield affinity values above $x \times 10^9 - x \times 10^{10}$. I am therefore satisfied that a challenge for insufficient disclosure based on failure to give full and frank disclosure of all steps necessary to achieve the claimed affinity values had first been sounded in PS 2. Admittedly, the thrust of the challenge at that time was different because table 17 was still described as disclosing affinity values.

71 Since then, the description of table 17 had been corrected and the table is now described as showing avidity values. Quite naturally, the objection based on the failure to disclose all necessary steps will have to be recast. This is unsurprising. The recast arguments were first made in the applicant's written submissions filed on 15 December 2014. Notwithstanding the fact that parties exchanged written submissions and hence the proprietor could not have responded to the recast arguments in their written submissions, the fact remains that the proprietors knew of this change. The proprietor could have put in written submissions to address these arguments before withdrawing from the hearings. Had it done so, any written submissions on record would still be considered by me in coming to a decision (since these are not testamentary evidence that have to be excluded). As it stands, the written submissions put in by the proprietor on 15 December 2014 do not deal with the recast arguments.

Conclusions on Insufficient Disclosure

72 For the purposes of this case, we need only consider the plain wording of section 80(1)(c) of the Act: "the specification of the patent does not disclose the invention clearly and completely for it to be performed by a person skilled in the art". To my mind, the applicant succeeded in its challenge for insufficient disclosure for the following reasons.

73 First, as pointed out by Dr Deonarain, there is a disjoint between the process described in example 39 – which will yield *affinity* binding – and table 17 which is intended to show the binding strength that is achieved by this process. Instead of showing *affinity* constants (which is what the reader would expect following from the preceding process description), table 17 shows *avidity* constants. There is a disjoint between the process described in Example 39 and the results shown in table 17. Hence, the method that had been disclosed in example 39 is incomplete as it cannot yield the results shown in table 17. There are steps missing. Therefore, this makes the case for insufficient disclosure.

74 Second, assuming that the disclosures are complete, since table 17 has now been corrected to disclose avidity constants, there is nothing in SG 905 to show that the methods disclosed will yield affinity constants with the values as claimed in Claims 1 and 10. Binding values (whether affinity or avidity) and rate constants are disclosed in tables 17 to 21 in SG 905. Except for table 18 which discloses affinity values for example 40, all the remaining tables disclose avidity values. As noted above, the affinity values disclosed in table 18 are about two orders of magnitude lower (i.e. $x \times 10^7 – x \times 10^8$) than those claimed in Claims 1 and 10 (i.e. $x \times 10^9 – x \times 10^{10}$). Since table 18 is the only set of affinity values disclosed, SG 905 failed to disclose all the steps necessary to achieve affinity values at the levels claimed in Claims 1 and 10. There is insufficient disclosure because the method disclosed only yields affinity values in the range $x \times 10^7 – x \times 10^8$. There are no instructions that a reasonably skilled technician may follow in order to achieve yields of antigens with affinity values of the magnitude claimed in Claims 1 and 10.

75 Third, there is nothing in the specifications that discloses experiments demonstrating that the method in SG 905 could achieve increasing levels of affinity bonding strength. Patent claims are to be understood by adopting a purposive approach addressed to the man skilled in the art as this strikes the best balance between the rights of the proprietor and third parties: ***FE Global Electronics Pte Ltd and others v Trek Technology (Singapore) Pte Ltd and another appeal*** [2006] 1 SLR(R) 874; [2005] SGCA 55. Adopting a purposive interpretation of Claims 1 and 10, I agree with Dr Deonarain that what is claimed by the proprietor is that the method will yield antibodies with affinity values no lower than $x \times 10^9 – x \times 10^{10}$ and the methods taught in SG 905 should yield increasing levels beyond this. In my perusal of the specifications, I have not been able to locate any table disclosing data that show increasing affinity values. I am not able to say whether the reasonably skilled technician on reading SG 905 would understand that there is a natural upper limit to the affinity binding strength that can possibly be achieved, e.g. as determined by the laws of physics or biochemistry. However, I think it reasonable and do accept Dr Deonarain's evidence that the reasonably skilled technician should not be required to conduct experiments in order to discover the limits of the methods taught in SG 905. I therefore conclude that there has not been sufficient

– or indeed any – disclosure of the data that is necessary to support claims that the method in SG 905 is capable of achieving affinity binding strengths beyond $x \times 10^9 – x \times 10^{10}$, without having to go so far as to say that no upper limits had been claimed by the proprietor.

76 Finally, I agree with Dr Deonarain that the data disclosed in specifications relate to experiments conducted on the CD4 human globular protein. A plain reading of Claims 1 and 10 discloses to me that the method yields antibodies that can target "a predetermined human antigen". I think that this could have either of two possible meanings: first, that the antibody obtained from the method taught by SG 905 can target all types of human antigens or second, that variations in the methods will yield antibodies capable of targeting different types of human antigens. The experimentation data relate to human globular proteins and I think that it would have been reasonable to limit the claims to human antigens with these structural properties. Otherwise, the reader may expect that the method should teach how different types of human antigens can be targeted by variations of parameters in the method taught by SG 905. What is clearly not disclosed is that the antibody produced by the method taught in SG 905 can target all types of human antigens. Thus, I agree with Dr Deonarain's critique that the methods disclosed in SG 905 are insufficient to achieve antibodies that can target other forms of human antigens beyond antigens with a globular structure.

Ground of Revocation under Section 80(1)(a)

77 Section 80(1)(a) of the Act reads:

> 80. —(1) Subject to the provisions of this Act, the Registrar may, on the application of any person, by order revoke a patent for an invention on (but only on) any of the following grounds:
>
> (*a*) the invention is not a patentable invention;
>
> …

Section 13(1) of the Act reads:

> 13. —(1) Subject to subsection (2), a patentable invention is one that satisfies the following conditions:
>
> …
>
> (*b*) it involves an inventive step; …

Section 15 of the Act reads:

> 15. An invention shall be taken to involve an inventive step if it is not obvious to a person skilled in the art, having regard to any matter which forms part of the state of the art by virtue only of section 14(2) and without having regard to section 14(3).

Lack of Inventive Step

SG 905 no more than a continuation of the experiments in the D8 patent

78 I turn now to the second ground of challenge, i.e. the lack of inventive step. Dr Deonarain's evidence may be summarised as follows. The authors of the D8 patent are the same as for SG 905: Nils Lonberg and Robert Kay are cited as inventors of both the SG 905 and the D8 patents, except that for SG 905, there is an additional inventor Ms Diane Fishwild. Based on his perusal of both patents, Dr Deonarain expressed the view that the background for both the SG 905 and D8 patents were word-for-word the same; both presenting the same problem to be solved. He also found that the summaries of invention for both patents were the same. The D8 patent also suggested high affinity bonding. The D8 patent taught the same problem and presented the same solution as SG 905; in fact, 35 examples in SG 905 were identical to those in the D8 patent. At the hearing, Dr Deonarain illustrated this point by pointing out example 33 in the D8 patent and example 34 in SG 905; these were word-for-word the same. The differences came towards the end of the specifications: SG 905 suggested that there were more ways to get DNA into cells. Dr Deonarain expressed the view that it appeared that the inventors carried out a series of experiments and filed patents at certain junctures. It appeared to him that after they had filed the D8 patent, they carried on with their experiments and eventually filed SG 905.

79 This part of Dr Deonarain's evidence is corroborated by the opinion of the patent examiner in the re-examination report. In respect of SG 905 being a continuation of experiments in the D8 patent, she states:

> The examiner takes the following position. The invention in 51905 is the result of a continued R+D project aimed at providing, and continuously improving a technology comprising transgenic animals capable of producing fully human therapeutic antibodies. The inventors of D8 and 51905 are the same. D8 and 51905 are concerned with the same long-term aim. D8 deals with essentially one aspect of the project: diversity of the immune response.

Increasing diversity to improve the therapeutic effect of antigens

80 Dr Deonarain opined that the idea of increasing diversity in order to produce better antibodies was already known in the prior art at that time. As I understand it, increasing the diversity leads to increased effectiveness of antibodies as they can bind to more types of antigens. Diversity is increased by the introduction of genetic material. This occurs naturally as the immune system is exposed to different types of antigens. In a laboratory environment, this occurs when genetic material from different types of organisms is introduced. Dr Deonarain cites as an example an article by Andrew Griffiths, *et al*, "Isolation of high affinity human antibodies directly from large synthetic repertoires" published in *The EMBO Journal* Vol 13 No 14 pp 3245 – 3260 in 1994 (a year before the priority date of 10 October 1995 claimed by SG 905). The authors state:

> In the immune system, antibodies with moderate affinities are selected from primary repertoires, and their affinities improved step-wise by rounds of somatic mutation and selection. However, theoretical arguments based on the idea of 'shape space' have suggested that *larger and more diverse repertoires should give rise to higher affinity antibodies* (Perelson and Oster, 1979).
>
> [Emphasis added.]

81 A further example was offered. The authors of JD Marks, *et al* "By-passing Immunization Human Antibodies from V-gene Libraries Displayed in Phage" *J Mol Biol* (1991) 222, 581 – 597, state at p 594:

> We attempted to maximise the size of the library by using a pUC-based phagemid (Hoogenboom *et al*, 1991) that has higher transformation efficiencies than fd vectors. Indeed our library sizes (107 to 108 members) were at least an order of magnitude greater than with phage fd (Clackson *et al*, 1991).

82 Dr Deonarain pointed out that the inventors' own D8 patent was the closest piece of prior art to SG 905. Dr Deonarain summarises that the D8 patent already taught the expansion of repertoire by introducing the YAC genes to the KCo4 mice. Although the D8 patent was principally concerned with the KCo4 transgene consisting of DNA from the Plasmid pKC1B and pKV4, the inventors had introduced genes from the YAC 4x17E1 clone into it in example 33 of the D8 patent. In SG 905, they started referring to this as the KCo5 mice: i.e. the KCo5 transgene consisting of DNA from the Plasmid pKC1B and pKV4 *and* the 450 kb YAC clone 4x17E1. In light of the general knowledge at that time as stated in *Griffiths*, Dr Deonarain's view was that the schooled person will find the introduction of the YAC genes in order to increase the diversity of the light chain for the purpose of increasing affinities to be an obvious step.

83 In respect of the D8 patent teaching the method of producing the KCo5 mice and increasing diversity to achieve better therapeutic effect, the patent examiner is similarly of the view that this would have been obvious to the reasonably skilled technician reading D8:

> According to the Applicant the skilled person, would also know from D8 and common general knowledge, how to increase the genetic diversity of the transgenic mice by cross breeding mice containing light chain transgenes encoded in … YAC4x17E1 (the KCo5 mice disclosed in D8) with the basic HC2 mice containing heavy chain transgenes (D8, Example 33). Further, a skilled researcher would have had the motivation to do so, because it was clear that more genetic diversity would lead to an increased probability of creating an antibody with higher affinity for any antigen …
>
> In view of the above, the examiner agrees with the Applicant, that a man skilled in the art would be in the possession of the KCo5 technology, and he would know that

> replacing the KCo4 parent in the KCo4 × HC2 cross with a KCo5 parent will increase the probability of producing antibodies with superior therapeutic utility.

SG 905 no more than routine analysis of the D8 patent

84 Dr Deonarain pointed out that after the correction of table 17, SG 905 could only demonstrate affinity binding strength in the range $x \times 10^7 - x \times 10^8$, essentially what is disclosed in the D8 patent. The only difference being that SG 905 proceeded to verify the experiment on the CD4 human protein.

85 Considering the D8 patent, I found corroboration of Dr Deonarain's evidence on this point at p 202, ln 30, *et seq*:

> The association and dissociation rates of the immunising human CD4 antigen for the monoclonal antibodies secreted by two of the hybridomas, 4E4.2 and 2C5.1, were determined. *The experimentally-derived binding constants (K_a) were approximately 9 × 10^7 M^{-1} and 8 × 10^7 M^{-1} for antibodies 4E4.2 and 2C5.1, respectively.* These K_a values fall within the range of murine IgG anti-human CD4 antibodies that have been used in clinical trials by others (Chen et al (1993) Int Immunol 6: 647).
>
> [Emphasis added.]

86 Similarly, claim 31 of the D8 patent echoes the same values for affinity binding constant:

> A hybridoma of Claim 28, wherein the monoclonal antibody binds to a human antigen with an affinity of at least 1×10^7 M^{-1}.

87 The patent examiner also reached a similar conclusion in her re-examination report. First, she adopted the proprietor's description of the inventive concept in SG 905, which is set out as follows:

> (a) Creation of the KCo5 transgene;
>
> (b) Creation of the KCo5 mouse by introducing the YAC genes;
>
> (c) Overcoming technical hurdles to create KCo5 transgenic mouse by a specifically designed "triangular gel tray"; and
>
> (d) Verifying that the additional YAC genes are present in human antibodies generated by the KCo5 mouse by testing against the human CD4 antigen.

88 The patent examiner then goes on to make the observation that steps (a) – (c) were already disclosed in the D8 patent and that step (d) was no more than a routine analysis to ensure that the YAC genes introduced into the KCo5 mouse was indeed incorporated into the human antigens that it generated. The routine analysis was conducted by testing the antigen against the human CD4 protein:

> The examiner takes the following position. The Proprietor has identified steps [(a) – (d)] as the novel technical elements, which the skilled person would have to devise in order to arrive at the inventive concept of [SG 905]. However, steps [(a) – (c)] had already been clearly disclosed in D8, and step [(d)] is a routine analysis, whether the transgene is functional in the host. Step [(d)] alone or combined with steps [(a) – (c)] cannot be regarded as involving an inventive step. It would have been obvious for one skilled in the art to cross the KCo5 mice of D8 to HC2 mice, in order to obtain a source of hybridomas, when whishing [*sic*] to increase the chances of obtaining fully human antibodies with superior therapeutic utility, such as an increased binding affinity.

Conclusions on Lack of Inventive Step

89 The lack of inventive step, or the obviousness of the claimed invention, is analysed using the 4-step approach laid down by the UK Court of Appeal in the case of ***Windsurfing International Inc v Tabur Marine (Great Britain) Ltd*** [1985] RPC 59. This has been adopted locally in ***Ng Kok Cheng v Chua Say Tiong*** [2001] 2 SLR(R) 326, ***Trek Technology (Singapore) Pte Ltd v FE Global Electronics Pte Ltd*** [2005] 3 SLR(R) 389 ("***Trek Technology***") ; [2005] 3 SLR 389, ***Mühlbauer AG v Manufacturing Integration Technology Ltd*** [2010] 2 SLR 724; [2010] SGCA 6 and other cases ("***Mühlbauer")***. In *Trek Technology*, as cited in *Mühlbauer* (at [20]), the *Windsurfing* test was formulated in the following manner:

> (a) Identify the inventive concept embodied in the patent in suit.
>
> (b) The court then assumes the mantle of the normally skilled but unimaginative addressee in the art at the priority date, imputing to him what was, at that date, common general knowledge in the art in question.
>
> (c) Identify what, if any, differences exist between the matter cited as being "known or used" and the alleged invention.
>
> (d) The court then asks itself the question whether, viewed without any knowledge of the alleged invention, those differences constitute steps which would have been obvious to the skilled man or whether they require any degree of invention.

90 **Step (a).** In its counter statement, the inventive concept described by the proprietor may be summarised as follows. The generation of fully human immunoglobulins with high affinity constant by using a transgenic mouse which contains transgenes created by microinjecting gene segments into a mouse embryo pro-nucleus. The patent examiner adopted the proprietor's description of the inventive concept: "the inventive concept is the provision of fully human antibodies with high K_a of at least 2×10^9 M^{-1} or at least 1×10^{10} M^{-1} produced from non-human animal B cells." Based on my understanding of SG 905, the inventive concept is (a) fully human antibodies with (b) high affinity constant that is (c) produced by the introduction of human transgenes into a mouse.

91 **Step (b).** The proprietor's D8 patent is heavily relied on by both Dr Deonarain and the patent examiner as the key piece of prior art. In summary, my conclusions with respect to the state of the art are as follows. The D8 patent teaches the introduction of human YAC genetic material into a mouse in order to produce transgenic antibodies: example 33 of the D8 patent. Such antibodies had been tested to yield affinity binding values in the range of 9×10^7 M^{-1} and 8×10^7 M^{-1}. The D8 patent claims affinity values of "at least 1×10^7 M^{-1}." These antibodies are also known to bind with human CD4 antigens. The prior art also taught that effectiveness of antibodies can be improved by introducing different types of genetic material.

92 **Step (c).** In its counter-statement, the proprietor identified that the prior art failed to teach or suggest fully human antibodies or human antibodies with the claimed high affinity for binding to human antigen. The applicant's position is that the steps required to be followed in order to produce the KCo5 mouse had already been disclosed in the D8 patent. They point to example 22 of the D8 patent as the operative section that teaches how to produce the KCo4 transgene. Examining both patents, I found example 22 in the D8 patent and SG 905 to be identical. In fact, the examples that follow are also identical, except that in the D8 patent, two different sets of examples were numbered 28 so the numbering of the examples diverged from example 28 onwards. In summary, the relevant sections of the D8 patent that teach the production of a transgenic mouse harbouring a human light chain minilocus (example 25), that can form antibodies comprising a functional human chain (example 26) containing a human heavy chain transgene and a human light chain transgene (example 27) are identical to the corresponding examples in SG 905.

93 Example 30 in the D8 patent (identical to example 31 of SG 905) teaches the production of fully human antibodies in the somatic chimeric mice. Hence, the claimed fully human antibody produced by the KCo5 mouse could already be obtained by following the steps taught in the D8 patent. The patent examiner had reached the same conclusion that SG 905 is a continuation of experiments to produce "fully human therapeutic antibodies." My conclusion is that insofar as the claimed invention in SG905 is that it teaches the production of fully human transgenic antibodies, then this has to fail as it is already taught in the D8 patent.

94 After the correction to SG 905, there is nothing in SG 905 that supports the levels of affinity binding strength that are claimed. On the contrary, the affinity binding values in SG 905 are within the range claimed by the D8 patent. I have evaluated Dr Deonarain's expert opinion above (paragraph 63, *et seq*) and do agree and adopt his conclusions. In respect of the claimed fully human antibody and the claimed high affinity binding, I am unable to identify anything that existed in the prior art that is different from the alleged invention that is claimed in SG 905.

95 The patent examiner identified an additional difference in SG 905 from the D8 patent, which is that the KCo5 mouse (which contains human light chains) was crossed with the HC2 mouse (which contains human heavy chains).

96 **Step (d).** As noted by both Dr Deonarain and the patent examiner, SG 905 appears to be a continuation of experiments following from the D8 patent by conducting systematic tests to ensure that the human genetic material was incorporated in the transgenic antibody and effective against the CD4 human globular antigen. My examination of the D8 patent revealed that there had already been tests conducted on the KCo4 chimeric mouse in order to demonstrate its capacity to form human antibodies in response to human-derived immunogen CD4 and its suitability as a source for making hybridomas secreting human sequence monoclonal antibodies reactive with human antigens: example 36. Perhaps the tests in SG 905 were more comprehensive as tests were conducted on both naturally occurring and recombinant CD4: table 19. In any event, the tests did not yield results that support the high levels of affinity binding strength that was claimed.

97 Dr Deonarain had opined that the prior art taught that increasing the diversity of antibodies can lead to improved effectiveness of antibodies. The patent examiner had concluded in the re-examination report that it would have therefore been obvious to cross the KCo5 mouse with a HC2 mouse in search of increasing diversity. Based on my understanding of the state of the art, I agree and adopt the patent examiner's conclusion that crossing a KCo5 mouse with a HC2 mouse would have been an obvious step for the reasonably skilled technician to take in order to increase diversity.

98 Accordingly, I conclude that SG 905 lacks inventiveness.

Conclusion

99 For all the reasons stated above, I find as follows:

(a) The amendments proposed by the proprietor should be allowed in the form set out in paragraph 24 above. The proprietor ought to be granted leave to amend the patent specifications. However, there is no necessity for the proprietor to file amended patent specifications in this regard in light of my subsequent finding.

(b) The application for revocation of claims 1 to 13 of SG 905 should be allowed for the reasons set forth in these grounds of decision. Therefore, the proprietor should file amended patent specifications for SG 905 omitting claims 1 to 13 pursuant to section 80(5)(b) of the Patents Act within 6 weeks of this decision.

(c) The Applicants are also entitled to costs to be taxed, if not agreed.

Dated this 23rd day of July 2015

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Yeong Zee Kin

IP Adjudicator

Intellectual Property Office of Singapore